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EXAMINER

HUYNH, PHUONG N

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/527,496	Applicant(s) TAHARA ET AL.	
	Examiner PHUONG HUYNH	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5 and 7-23 is/are pending in the application.
- 4a) Of the above claim(s) 1,3,4 and 11-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,7-10 and 20-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/11/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1, 3-5 and 7-23 are pending.
2. Claims 1, 3-4 and 11-19 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
3. Claims 5, 7-10, 20-22, and newly added claim 23 drawn to nonapeptide that reads on the elected species of SEQ ID NO: 30 and SEQ ID NO: 54, are being acted upon in this Office Action.
4. In view of the amendment filed February 19, 2008, the following rejections remain.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 5, 7-10, and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated nonapeptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 30 and SEQ ID NO: 54 wherein the peptide binds to HLA-A 0201 restricted T cell receptor with low affinity and induces high CTL response, (2) an isolated peptide consisting of the amino acid sequence of SEQ ID NO: 30 wherein the peptide has one or two amino acids substitution or addition and wherein the peptide binds to HLA-A 0201 restricted T cell receptor with low affinity, and induces high CTL response, (3) the isolated peptide mentioned above wherein the peptide has the amino acid sequence of SEQ ID NO: 54, and wherein the second amino acid from the N terminus is leucine. (4) the isolated peptide mentioned above wherein the C-terminal amino acid is valine or leucine and (5) a composition comprising one or more peptide mentioned above for inducing cytotoxic T cell, **does not** reasonably provide enablement for (1) any nonapeptide or decapeptide as set forth in claims 5 and 7, (2) any pharmaceutical composition for treating and/or preventing any tumors as set forth in claim 9, (3) any pharmaceutical composition for treating any diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis as set forth in claim 10,

Art Unit: 1644

(4) any vaccine for inhibiting angiogenesis as set forth in claims 20-21 and (5) any peptide wherein said peptide has an amino acid sequence as set forth in SEQ ID NO: 54. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 5 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claim 7 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function wherein the second amino acid from the N terminus is leucine or methionine.

Claim 8 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function wherein the C-terminal amino acid is valine or leucine and/or wherein the second amino acid from the N terminus is leucine or methionine.

Claim 9 is broadly drawn to a pharmaceutical composition for treating and/or *preventing* any and all tumors comprising a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino

Art Unit: 1644

acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claim 10 is broadly drawn to a pharmaceutical composition for treating any diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis comprising a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claims 20-22 are broadly drawn to a vaccine for inhibiting angiogenesis at a diseased site wherein the vaccine comprises a genus of isolated nonapeptide or decapeptides consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 29, 30, 33, 34, 40 or 46 or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility wherein one or two amino acids have been substituted with any amino acids or any one or two amino acids have been added to the amino acid sequence of SEQ ID NO: 29, 30, 33, 34, 40 or 46 as an active ingredient.

Claim 23 encompasses a peptide that has *an* amino acid sequence set forth in SEQ ID NO: 54 or a peptide shorter than SEQ ID NO: 54.

Enablement is not commensurate in scope with how to make and use a genus of peptide mentioned above as a pharmaceutical composition to *prevent* tumor or to treat any diseases mentioned above or as a vaccine for inhibiting angiogenesis.

The specification discloses only the specific nanopeptides from human KDR such as the ones shown in Table 2 and Table 4. Cytotoxic T cell recognition of these peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 5, 8, 11 and 12 from KDR is restricted to HLA-A2402 (Table 1) and these peptide bind to T cell receptor with high affinity. Cytotoxic T cell recognition of these peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 29, 30, 33, 34, 40 and 46 from KDR is restricted to HLA-A20201 (Table 4) and these peptide bind to T cell receptor with low affinity. However, these low affinity peptide induces high level of CTL response as measured by IFN γ ELISPOT *in vitro*, see page 19. These peptides were used to generate human CTL clones, see page 24 Table 7 or antigen presenting cell.

At the time of filing, the specification does not teach how to make any peptides as set forth in claims 5, 7-10, and 20-22 wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30. The term “having” is open-ended. It expands the

Art Unit: 1644

peptide to include additional amino acids at either or both ends. Further, there is insufficient guidance as to the structure of the peptide after which two amino acids have been substituted other than the specific SEQ ID NO: 54 or added and still induces T cell response.

Further, pharmaceutical composition in the absence of *in vivo* working examples are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the peptide may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the peptide unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). As such, it is unpredictable such peptide is efficacious in treating any diseases as set forth in claim 10, much less for preventing any tumor in the absence of *in vivo* working example.

The state of the art as taught by Leggett et al (of record, *J Immunology* 161: 4728-4735, 1998; PTO 892) demonstrates that nonconservative changes in amino acid side chains, which apparently do not interact directly with the T cell receptor can also influence TCR recognition of MHC class I/peptide complex. Leggett et al show that single amino acid substitution does not always allow the prediction of the outcome of double substitutions and that CTL silenced by a single mutation can be reengaged by a compensating second substitution (see page 4728, col. 2, in particular).

Baxeavanis et al (of record, *Cancer Immunol Immunother* 55: 85-95, 2006; PTO 892) teach immunogenicity of a given CTL peptide does not necessarily correlate with increased affinity for binding to MHC class I alleles. For instance, HER-2 (10420) restricted by H-dDq was shown to generate CTL lines *in vitro*, which upon adoptive transfer could highly protect non-transgenic mice from spontaneous mammary carcinomas. However, when alanine was substitute for glutamate at position 2, this peptide demonstrated markedly improved recognition by a T cell clone. Given the numerous amino acids substitutions in SEQ ID NO: 30 and the term "having" is open-ended, it is unpredictable which undisclosed peptide still maintains TCR recognition, let alone induces high CTL activity.

With respect to pharmaceutical composition comprising any peptide for "preventing" tumors, there is insufficient *in vivo* working example showing any peptide mentioned above could

Art Unit: 1644

treat any and all tumors, much less “preventing” any tumors from happening. The specification fails to provide guidance and in vivo working example as how to select or identify an individual before tumors set in, how to predict who would or would not have which type of cancers, let alone administering which peptide in such individual could prevent any tumors or cancer from happening.

With respect to vaccine for inhibiting angiogenesis at a disease site, because KDR is a self peptide, there is insufficient guidance and in vivo working example showing any peptide can mount a cytotoxic T cell response against self antigen, in turn, effect to prevent any and all cancer from happening in animal.

Baxevanis et al (of record, Cancer Immunol Immunother 55: 85-95, 2006; PTO 892) teach vaccination studies in animals utilizing HER-2/neu peptides have been successful in eliminating tumor growth. In humans, however, although immunological responses against the peptides used for vaccination, no clinical responses have been described. Because HER-2 receptor, like KDR receptor is a self-antigen, functional immune responses against it may be limited through tolerance mechanism (see abstract, in particular).

Mestas et al (of record, J Immunology 172: 2731-2738, 2004; PTO 892) teach there are differences between mouse and human immunology. As therapies for human diseases become ever more sophisticated and specifically targeted, it becomes increasingly important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with examples of therapies that work well in mice but fail to provide similar efficacy in humans (see entire document, page 2731, col. 2, in particular).

Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants’ arguments filed February 19, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Applicants have replaced the open language "comprising" with the closed language "consisting of" and limited the number of amino acid residues to be substituted or added to "one or two." While this amendment should not be construed as Applicants' agreement with or acquiescence to the Examiner's position regarding the alleged lack of enablement, Applicants nevertheless submit that such an amendment renders moot the Examiner's concerns regarding enablement of the claimed invention.

Moreover, Applicants submit that one of ordinary skill in the art would readily recognize how to make and use the invention presently claimed (*e.g.*, nonapeptides and decapeptides consisting of SEQ ID NOs: 29, 30, 33, 34, 40, and 46, optionally have one or two substitutions or additions) from the disclosures in the present specification coupled with information known in the art without undue experimentation and with a reasonable expectation of success. For example, on the issue of peptide analogues having one or two amino acid substitutions, it was well known in the art at the time of filing of the present application that the HLA-A2 binding affinity of epitope peptides could be maintained or enhanced after replacement at position 2 or C-terminal anchor residues (*see, e.g.* page 7, lines 14-17 of the present specification and Rammensee *et al.*, *Immunogenetics*, 1995, 41: 178-228 (for example, page 193, Table 2B); Kubo *et al.*, *J. Immunol.*, 1994, 152:3913-3924 (for example, right column of page 3915, lines 6-12 from the bottom); and Falk *et al.* *Nature* 1991, 351:290-296 (for example, left column of page 293, lines 6-7 and Table 4 (not cited)).

In addition, Zaremba *et al.* in *Cancer Res.* 1997, 57:4570-4577 (for example, left column of page 4572, lines 4-10 and line 21 to right column, line 1 (not cited) demonstrate that the CTL inducibility of an epitope peptide can be maintained or enhanced by the replacement of an amino acid residue at any one of positions 5-7 in the original epitope peptide. Further, it is reported that epitope peptides also maintained their CTL inducibility after substitution of amino acid residue at various positions in several publications. *See, e.g.*, Hoffmann *et al.*, *J Immunol.* 2002, 168(3): 1338-47 (for example, page 1344 2nd paragraph of Discussion); Dionne *et al.*, *Cancer Immunol Immunother.* 2003, 52:199-206 (for example, right column of page 204, 4th paragraph); and Dionne *et al.* *Cancer Immunology, Immunotherapy* 2004, 53:307-314 (for example, right column, 1st and 2nd paragraph).²

In the present application, the maintained CTL inducibility of a peptide analogue of which one amino acid residue is substituted at the N-terminal (SEQ ID NO: 54) was confirmed (*see, e.g.*, page 26, [Example 19] and Fig. 14).

Art Unit: 1644

V I A M F F W L L ;SEQ ID NO: 30

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V L A M F F W L L ;SEQ ID NO: 54

As for peptide analogues having one or two additional amino acid residues, it is generally accepted that such peptides will be digested in antigen presenting cells into nona- or deca- peptides, and will then bind with HLA to be presented on the surface of the cells. Thus, the resulting peptides which are presented in a HLA complex are the same as the original peptides. Accordingly, at the time of filing, once epitope peptides whose CTL inducibility has been confirmed are provided, a skilled artisan can obtain peptide analogues with maintained CTL inducibility by replacing or adding one or two amino acid residues to those epitope peptides without undue experimentation and with a reasonable expectation of success.

The Examiner is respectfully reminded that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, provided it is merely routine. *See, In re Wands* 8 U.S.P.Q. 1400, 1404 (Fed. Cir. 1988). In this case, Applicants submit the "trial and error" testing needed to identify regions of the peptide that can tolerate mutation is within the parameters of routine experimentation and optimization.

With respect to the Examiner's concerns regarding the unpredictability of "prevention" in the context of claim 9 on page 9 of the present Office Action, Applicants submit the Examiner's interpretation of the term "prevent" is unduly narrow. According to www.wikipedia.org, "in medicine, prevention is any activity which reduces the burden of mortality or morbidity from disease". Prevention can occur "at primary, secondary and tertiary prevention levels." While primary prevention avoids the development of a disease, secondary and tertiary levels of prevention encompass activities aimed at preventing the progression of a disease and the emergence of symptoms as well as reducing the negative impact of an already established disease by restoring function and reducing disease-related complication

Accordingly, Applicants respectfully submit that, contrary to the Examiner's implication, the term "prevent," when afforded its ordinary and customary meaning, does not necessarily equate to absolute cessation. Moreover, Applicants respectfully submit that one skilled in the art would readily recognize that, in the context of the instant claims, prevention encompasses a wide range of prophylactic therapies aimed at alleviating the severity of the

Art Unit: 1644

particular disorder, *e.g.* reducing the proliferation and metastasis of tumors, reducing angiogenesis, etc. Accordingly, Applicants submit that one of ordinary skill in the art would be able to "treat and prevent" tumors in accordance with the method of claim 9 without undue experimentation.

In response, claims 5, 7-10, and 20-22 are broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide "having an amino acid sequence" larger than SEQ ID NO: 29, 30, 33, 34, 40 or 46 or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility wherein one or two amino acids have been substituted with any amino acids or any one or two amino acids have been added to the amino acid sequence of SEQ ID NO: 29, 30, 33, 34, 40 or 46. Claim 23 encompasses a peptide that has the amino acid sequence set forth in SEQ ID NO: 54 or a peptide shorter than SEQ ID NO: 54.

Although claim 5 has been amended, the term "having *an* amino acid sequence" encompasses a peptide longer than any of the amino acid sequence recited in claim 5 such as SEQ ID NO: 30, a peptide shorter than any of the amino acid sequence recited in claim 5 such as SEQ ID NO: 30. None of the peptides disclosed in the specification are longer than 10 amino acids in length. The term "having" is open-ended. It expands the recited peptide such as SEQ ID NO: 30 to include additional amino acids at either or both ends. There is insufficient guidance and *in vivo* working example about the structure associated with function of any peptide having the amino acid sequence longer than SEQ ID NO: 30, and still binds to T cell receptor and/or induce cytotoxic immune response.

In the alternative, the peptide in the amended claims 5 and newly added claim 23 could also be shorter than the recited SEQ ID NO: because the term "*an* amino acid sequence". Neither the specification as filed nor the art teach any MHC peptide shorter than 9 amino acids in length such as 7, 6, 5, 4, 3 or 2 amino acids in length still binds to the T cell receptor. Amending claim 23 to recite "The peptide of claim 5, wherein said peptide has the amino acid sequence as set forth in SEQ ID NO: 54" would obviate this rejection.

With respect to "a peptide with cytotoxic T cell inducibility" in claim 5, it is not clear if the peptide is even derived from SEQ ID NO: 30. A peptide without the amino acid sequence has no structure, much less function.

With respect to peptide wherein one or two amino acids have been substituted to the amino acid sequence of SEQ ID NO: 30, there is insufficient guidance as to which amino acids within the length of SEQ ID NO: 30 to be substituted other than SEQ ID NO: 54 for which amino

Art Unit: 1644

acid such that the resulting peptide still binds to T cell receptor, in turn, maintaining cytotoxic T cell inducibility. At the time of filing, there is no closure of any peptide longer than 9 amino acids in the specification as filed.

It is known in the art that substituting amino acids such as the anchor residues would result in lost of T cell receptor binding and depending on the type amino acid being substituted, the peptide could resulted in complete loss of binding capacity.

Kubo *et al.* (*of record*, *J. Immunol.*, 1994, 152:3913-3924 (for example, left column of page 3918, last paragraph from the bottom). Note, amending the claim 5 to recite functional language in addition to one or two amino acids have been substitute or added to the amino acid sequence of SEQ ID NO: 30 would obviate this rejection, see item 6 above.

With respect to pharmaceutical composition in claim 8, pharmaceutical composition in the absence of in vivo working examples are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the peptide may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the peptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). As such, it is unpredictable such peptide is efficacious in treating any diseases as set forth in claim 10, much less for preventing any tumor in the absence of in vivo working example. Note, amending the claim to recite a composition comprising one or more peptides wherein the peptide consisting of the amino acid sequence of SEQ ID NO: 30 and SEQ ID NO: 54 would obviate this rejection since one of skill in the art can use the peptide to induce CTL immune response in vitro.

With respect to pharmaceutical composition for treating various diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis as recited in claim 10, the specification discloses inducing CTL in vitro and it is not clear the reliance of in vitro inducing CTL response is an appropriate model for treating diabetic retinopathy and/or autoimmune diseases such rheumatoid arthritis, psoriasis or atherosclerosis. Given the lack of guidance, direction and insufficient *in vivo* working examples, the breadth of the claims, which encompass innumerable possible peptides and diseases prevention, and the amount of experimentation

required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

7. Claims 5, 7-10, and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 5 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claim 7 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function wherein the second amino acid from the N terminus is leucine or methionine.

Claim 8 is broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function wherein the C-terminal amino acid is valine or leucine and/or wherein the second amino acid from the N terminus is leucine or methionine.

Claim 9 is broadly drawn to a pharmaceutical composition for treating and/or *preventing* any and all tumors comprising a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claim 10 is broadly drawn to a pharmaceutical composition for treating any diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis comprising a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid

Art Unit: 1644

sequence” larger than SEQ ID NO: 30, or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility, or any peptide having one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: 30 without any function.

Claims 20-22 are broadly drawn to a vaccine for inhibiting angiogenesis at a diseased site wherein the vaccine comprises a genus of isolated nonapeptide or decapeptide consisting of a peptide “having an amino acid sequence” larger than SEQ ID NO: 29, 30, 33, 34, 40 or 46 or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility wherein one or two amino acids have been substituted with any amino acids or any one or two amino acids have been added to the amino acid sequence of SEQ ID NO: 29, 30, 33, 34, 40 or 46 as an active ingredient.

Claim 23 encompasses a peptide that has *an* amino acid sequence set forth in SEQ ID NO: 54 or a peptide shorter than SEQ ID NO: 54.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., complete or partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, method of making the claimed invention, level of skill and knowledge in the art and predictability in the art sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF’s were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification does not reasonably provide a **written description** for (1) a genus of peptide with cytotoxic T cell inducibility without the amino acid sequence, (2) a genus of isolated nonapeptide or decapeptide consisting of a peptide “*having an amino acid sequence*”

Art Unit: 1644

larger than SEQ ID NO: 30, (3) a genus of peptide having an amino acid sequence shorter than SEQ ID NO: 30, (4) a genus of peptide wherein one or two amino acids have been substituted to the amino acid sequence of SEQ ID NO: 30, and (4) a genus of peptide shorter than SEQ ID NO: 54, (5) a pharmaceutical composition for preventing tumors or treating various diseases such as the ones recited in claim 10 and (6) a vaccine comprising any peptide mentioned above.

At the time of filing, the specification discloses only the specific nanopeptides from human KDR such as the ones shown in Table 2 and Table 4. These CTL epitopes restricted to HLA-A2402 consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 5, 8, 11 and 12 as shown in Table 1. These peptides bind to T cell receptor with high affinity. However, peptide restricted to HLA-A20201 consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 29, 30, 33, 34, 40 and 46 binds to T cell receptors with low affinity, see page Table 4. These low affinity peptides induce high level of CTL response as measured by IFN γ ELISPOT *in vitro*, see page 19. These peptides were used to generate human CTL clones, see page 24 Table 7 or generating antigen presenting cell (exosome).

Other than the specific peptide consisting of the amino acid sequence as set forth in SEQ ID NO: 29, 30, 33, 34, 40, 46 and 54 that induces cytotoxic T cell response *in vitro*, the specification does not adequately describe the structure associated with function of a genus of peptide with cytotoxic T cell inducibility.

With respect to the term "having *an* amino acid sequence", none of the peptides disclosed in the specification are longer than 10 amino acids in length. The term "having" is open-ended. It expands the recited peptide such as SEQ ID NO: 30 to include additional amino acids at either or both ends. There is insufficient written description about the structure associated with function of any peptide comprising the amino acid sequence of SEQ ID NO: 30. Further, the peptide could also be shorter than the recited SEQ ID NO: because the term "*an* amino acid sequence". There is no disclosure of any peptide shorter than SEQ ID NO: 30 or SEQ ID NO: 54 such as peptide consisting of 7, 6, 5, 4, 3, 2 and 1 amino acid and still binds to T cell receptor, let alone still maintains its function, i.e., induces T cell cytotoxicity.

Further, the specification does not adequately describe any peptides as set forth in claims 5, 7-8, 9-10, and 20-22 wherein one or two amino acids have been substituted or added to the sequence recited in the claims. There is a lack of disclosure as to the structure of the peptide after one or two amino acids have been added or which amino acids within the nonapeptide or

Art Unit: 1644

decapeptide to be substituted other than SEQ ID NO: 54 such that the resulting peptide still binds to T cell receptor, in turn, induces cytotoxic T cell activity for use as a pharmaceutical composition or vaccine to prevent tumor.

Given the numerous substitutions and additions without any function, the final peptide would have no resemblance to the peptide consisting of the amino acid sequence of SEQ ID NO: 30, much less such peptide still induces CTL activity for treating and/or preventing any and all tumors or treating any diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis. Because the described peptides of SEQ ID NO: 30 and SEQ ID NO: 54 are not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus of modified peptide. Accordingly, one of skill in the art would conclude that applicant was not in possession of the claimed genus.

With respect to pharmaceutical composition for preventing tumors and vaccine, there is no *in vivo* working example of any peptide could treat any tumor, much less such peptide could prevent all tumors as a vaccine.

The specification discloses only 5 nonomers (9-mer peptides) from human KDR that bind to HLA-A0201 restricted T cell receptor with low affinity while having high CTL activity, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with cytotoxic T cell inducibility or any peptide longer than 9 or 10 amino acids in length or any peptide shorter than 9 amino acids to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed February 19, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the specification describes an isolated nonapeptide *consisting* o/the amino acid sequence of SEQ ID NO: 30 that binds to HLA-A 0201 and induces high CTL activity. *See*, pages 10-11 of the present Office Action. Solely in the interest of expediting prosecution, Applicants have replaced the open-end language "comprising" with the close-end language "consisting" and limited the number of amino acid residues to be substituted or added to

Art Unit: 1644

"one or two". Moreover, for the reasons discussed above, Applicants submit that one of ordinary skill in the art would readily recognize that Applicants were in possession of the invention presently claimed (e.g., nonapeptides and decapeptides consisting of SEQ ID NOs: 29, 30, 33, 34, 40, and 46, optionally have one or two substitutions or additions) from the disclosures in the patent coupled with information known in the art.

In response, claims 5, 7-10, and 20-22 are broadly drawn to a genus of isolated nonapeptide or decapeptide consisting of a peptide "having an amino acid sequence" larger than SEQ ID NO: 29, 30, 33, 34, 40 or 46 or any fragment thereof or a genus of peptide with cytotoxic T cell inducibility or any peptide mentioned above wherein one or two amino acids have been substituted with any amino acids or any one or two amino acids have been added to the amino acid sequence of SEQ ID NO: 30. Claim 23 encompasses a peptide that has the amino acid sequence set forth in SEQ ID NO: 54 or a peptide shorter than SEQ ID NO: 54.

Other than the specific peptide consisting of the amino acid sequence as set forth in SEQ ID NO: 29, 30, 33, 34, 40, 46 and 54, the specification does not adequately describe the structure associated with function of a genus of peptide with cytotoxic T cell inducibility.

With respect to the term "having *an* amino acid sequence", none of the peptides disclosed in the specification are longer than 10 amino acids in length. The term "having" is open-ended. It expands the recited peptide such as SEQ ID NO: 30 to include additional amino acids at either or both ends. There is insufficient written description about the structure associated with function of any peptide comprising the amino acid sequence of SEQ ID NO: 30. Further, the peptide could also be shorter than the recited SEQ ID NO: because the term "*an* amino acid sequence". There is no disclosure of any peptide shorter than SEQ ID NO: 30 or SEQ ID NO: 54 such as peptide consisting of 7, 6, 5, 4, 3, 2 and 1 amino acid and still binds to T cell receptor, let alone still maintains its function, i.e., induces T cell cytotoxicity.

Further, the specification does not adequately describe any peptides as set forth in claims 5, 7-8, 9-10, and 20-22 wherein one or two amino acids have been substituted or added to the sequence recited in the claims. There is a lack of disclosure as to the structure of the peptide after one or two amino acids have been added or which amino acids within the nonapeptide or decapeptide to be substituted other than SEQ ID NO: 54 such that the resulting peptide still binds to T cell receptor, in turn, induces cytotoxic T cell activity for use as a pharmaceutical composition or vaccine to prevent tumor.

Art Unit: 1644

Given the numerous substitutions and additions without any function, the final peptide would have no resemblance to the peptide consisting of the amino acid sequence of SEQ ID NO: 30, much less such peptide still induces CTL activity for treating and/or preventing any and all tumors or treating any diseases such as diabetic retinopathy, chronic rheumatoid arthritis, psoriasis, and atherosclerosis. Because the described peptides of SEQ ID NO: 30 and SEQ ID NO: 54 are not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus of modified peptide. Accordingly, one of skill in the art would conclude that applicant was not in possession of the claimed genus.

The state of the art as taught by Leggett et al (of record, J Immunology 161: 4728-4735, 1998; PTO 892) demonstrates that nonconservative changes in amino acid side chains, which apparently do not interact directly with the T cell receptor can also influence TCR recognition of MHC class I/peptide complex. Leggett et al show that single substitutions do not always allow the prediction of the outcome of double substitutions and that CTL silenced by a single mutation can be reengaged by a compensating second substitution (see page 4728, col. 2, in particular).

It is also known in the art that at the time the invention was made that substituting two amino acids located in the anchor residues of a T cell peptide resulted in lost of binding to T cell receptor. As such, the genus of peptide with one or two amino acids have been substituted is not adequately described.

With respect to pharmaceutical composition for preventing tumors and vaccine, there is not a single *in vivo* working example of using any peptide mentioned above to prevent any and all tumors. The specification discloses the use of peptide to induce cytotoxic T cell *in vitro*.

Finally, the specification discloses only 5 nonomers (9-mer peptides) from human KDR that bind to HLA-A0201 with high CTL activity, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide with cytotoxic T cell inducibility or any peptide longer than 9 or 10 amino acids in length or any peptide shorter than 9 amino acids to describe the genus. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Art Unit: 1644

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Flamme et al (of record, Developmental Biology 169: 699-712, 1995; PTO 892).

Amended claim 5 as written encompasses an isolated nonapeptide or decapeptide *having an amino acid sequence* of SEQ ID NO: 30 or a fragment thereof or any peptide with cytotoxic T cell inducibility or any peptide mentioned above wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ IDNO: 30.

Flamme et al teach a peptide such as quail FLK-1 and mouse FLK-1 (VEGFR-2) polypeptide comprising the amino acid sequence VIAMFFWLL, which is 100% identical to the claimed SEQ ID NO: 30 (see page 701, FIG4, residues 1-9 of the reference quail sequence and residues 771-779 of the reference mouse sequence, in particular). The term “having” is open-ended. It expands the claimed nonapeptide of SEQ ID NO: 30 to include additional amino acids at either or both ends to include the reference sequences. The reference polypeptide inherently has cytotoxic T cell inducibility since cytotoxic T cell recognizes and generates T cells epitope that is 9 ± 1 amino acids in length. The C terminal amino acid reference of the reference peptide is leucine (see sequences in Figure 4, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants’ arguments filed February 19, 2008 have been fully considered but are not found persuasive.

Applicants’ position is that amended claim 5 to set forth an isolated nonapeptide or decapeptide *consisting of* a peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO:30. Flamme does not disclose or suggest an isolated nonapeptide or decapeptide *consisting of* a peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO:30. Because Flamme does not disclose or suggest each and every element of the claimed peptide, Flamme does not anticipate the present invention.

In response, the term “having an amino acid sequence” encompasses a peptide larger than SEQ ID NO: 30 because the term “having” is still open-ended. Further, the term “or a peptide with cytotoxic T cell inducibility” encompasses any peptide with T cell inducibility and such peptide does not even have to come from SEQ ID NO: 30 so long it induces cytotoxic T cell activity.

10. Claims 5 and 8 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,712,380 (of record, issued January 27, 1998; PTO 892).

Amended Claim 5 as written encompasses an isolated nonapeptide or decapeptide *having an amino acid sequence* of SEQ ID NO: 30 or a fragment thereof or any peptide with cytotoxic T cell inducibility wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ IDNO: 30.

The ‘380 patent teaches a peptide such as SEQ ID NO: 15 comprising the amino acid sequence VIAMFFWLL, which is 100% identical to the claimed SEQ ID NO: 30 (see reference SEQ ID NO: 15, residues 772 to 781, in particular). The term “having” is open-ended. It expands the claimed nonapeptide to include additional amino acids at both ends to include the reference sequence. The reference polypeptide also anticipates the claimed peptide having two or more amino acids have been added to the amino acid sequence of SEQ ID NO: 30. The reference polypeptide inherently has cytotoxic T cell inducibility since cytotoxic T cell recognizes peptide and generates T cells epitope that is 9 ± 1 amino acids in length. The C terminal amino acid reference of the reference peptide is valine (see reference sequence SEQ ID NO: 15, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants’ arguments filed February 19, 2008 have been fully considered but are not found persuasive.

Applicants’ position is that amended claim 5 to set forth an isolated nonapeptide or decapeptide *consisting of* a peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO:30. Flamme does not disclose or suggest an isolated nonapeptide or decapeptide *consisting of a* peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have been substituted or added to the amino acid

Art Unit: 1644

sequence of SEQ ID NO:30. Because Flamme does not disclose or suggest each and every element of the claimed peptide, Flamme does not anticipate the present invention.

In response, the term “having an amino acid sequence” encompasses a peptide larger than SEQ ID NO: 30 because the term "having" is still open-ended. Further, the term “or a peptide with cytotoxic T cell inducibility” encompasses any peptide with T cell inducibility and such peptide does not even have to come from SEQ ID NO: 30 so long it induces cytotoxic T cell activity.

11. Claims 5 and 7-10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kubo et al (of record, J Immunology 152: 3913-3921, 1994; PTO 892).

Amended Claim 5 as written encompasses an isolated nonapeptide or decapeptide *having an amino acid sequence* of SEQ ID NO: 30 or a fragment thereof or any peptide with cytotoxic T cell inducibility wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ IDNO: 30.

Kubo et al teaches various human HLA-A24 nonamer peptides or decamers such as polyalanine analogue AAAAAAAAAA having various amino acid substitutions at position 1 through 9 and binds to T cell receptor (see entire document, page 3918, Table IV, page 3919, col., in particular). The reference peptide inherently induces T cell cytotoxicity since it binds to T cell receptor. Kubo et al teach the second amino acid from the N terminus is methionine (M) while the C-terminal amino acid is leucine (L), the peptide binds to HLA-A24 allele class I (see page 3920, Table V, in particular). Kubo et al teach the second amino acid from the N terminus is Leucine (L) while the C-terminal amino acid is Valine (V), the peptide binds to HLA-A2.1 allele class I (see page 3918, Table IV, in particular). Kubo et al teach a composition comprising the reference peptide in carrier such as DMSO/water (see page 3915, col. 1, peptide synthesis, in particular) or in PBS (see page 3914, col. 2, last paragraph, in particular). Claims 9-10 are included in this rejection because a composition is a composition irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed February 19, 2008 have been fully considered but are not found persuasive.

Applicants' position is that amended claim 5 to set forth an isolated nonapeptide or decapeptide *consisting of* a peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have

Art Unit: 1644

been substituted or added to the amino acid sequence of SEQ ID NO:30. Flamme does not disclose or suggest an isolated nonapeptide or decapeptide *consisting of a* peptide having the amino acid sequence of SEQ ID NO:30 or consisting of a peptide with cytotoxic T cell inducibility, wherein one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO:30. Because Flamme does not disclose or suggest each and every element of the claimed peptide, Flamme does not anticipate the present invention.

In response, the term “having an amino acid sequence” encompasses a peptide larger than SEQ ID NO: 30 because the term "having" is still open-ended. Further, the term “or a peptide with cytotoxic T cell inducibility” encompasses any peptide with T cell inducibility and such peptide does not even have to come from SEQ ID NO: 30 so long it induces cytotoxic T cell activity.

12. The following new ground of rejection is necessitated by the amendment filed February 19, 2008.
13. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
14. Claims 5 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is rejected because of improper Markush group "...selected from the group consisting of SEQ ID NO:40, **and** 46 **or** a peptide with ...". It is suggested that claim 5 be amended to recite "An isolated peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 40, SEQ ID NO: 46 and a peptide". Further, it is unclear the "one or two amino acids have been substituted or added to the amino acid sequence of SEQ ID NO: ...46" is referred to the nonapeptide or the decapeptide or the peptide with cytotoxic T cell inducibility. Correction is required.

Claim 7 is indefinite because the second amino acid from the N terminus of peptide of claim 5 such as SEQ ID NO: 30 is not leucine or methionine. The second amino acid from the N terminus of peptide consisting of the amino acid sequence VIAMFFWLL of SEQ ID NO: 30 is isoleucine (Ile).

Art Unit: 1644

15. No claim is allowed.
16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.
18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

July 7, 2008